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Non-adrenergic vasopressors for vasodilatory shock or perioperative vasoplegia: a meta-analysis of randomized controlled trials

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Abstract

Background Excessive exposure to adrenergic vasopressors may be harmful. Non-adrenergic vasopressors may spare adrenergic agents and potentially improve outcomes. We aimed to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy of non-adrenergic vasopressors in adult patients receiving vasopressor therapy for vasodilatory shock or perioperative vasoplegia.

Methods We searched PubMed, Embase, and Cochrane Library for RCTs comparing non-adrenergic vasopressors with adrenergic vasopressors alone or placebo in critically ill or perioperative patients. Each eligible study was categorized into septic shock, cardiac surgery, or non-cardiac surgery. Non-adrenergic vasopressors included vasopressin, terlipressin, selepressin, angiotensin II, methylene blue, and hydroxocobalamin. The primary outcome was mortality at longest follow-up. We conducted a random-effects meta-analysis. We registered the protocol in PROSPERO International Prospective Register of Systematic Reviews (CRD42024505039).

Results Among 51 eligible RCTs totaling 5715 patients, the predominant population was septic shock in 30 studies, cardiac surgery in 11 studies, and non-cardiac surgery in 10 studies. Cochrane risk-of-bias tool for randomized trials version 2 identified 17 studies as low risk of bias. In septic shock, mortality was significantly lower in the non-adrenergic group (960/2232 [43%] vs. 898/1890 [48%]; risk ratio [RR], 0.92; 95% confidence interval [95% CI], 0.86–0.97; $P=0.03$; $I^2=0\%$), with none of the individual non-adrenergic vasopressors showing significant survival benefits. No significant mortality difference was observed in patients undergoing cardiac surgery (34/410 [8.3%] vs. 47/412 [11%]; RR, 0.82; 95% CI, 0.55–1.22; $P=0.32$; $I^2=12\%$) or those undergoing non-cardiac surgery (9/388 [2.3%] vs. 18/383 [4.7%]; RR, 0.66; 95% CI, 0.31–1.41; $P=0.28$; $I^2=0\%$).

Conclusions Administration of non-adrenergic vasopressors was significantly associated with reduced mortality in patients with septic shock. However, no single agent achieved statistical significance in separate analyses. Although the pooled effects of non-adrenergic vasopressors on survival did not reach statistical significance in patients undergoing cardiac or non-cardiac surgery, the confidence intervals included the possibility of both no effect and a clinically important benefit from non-adrenergic agents. These findings justify the conduct of further RCTs comparing non-adrenergic vasopressors to usual care based on noradrenaline alone.

Keywords Meta-analysis, Catecholamines, Arginine vasopressin, Angiotensin II, Methylene blue, Mortality

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Background

Vasodilatory shock remains a clinical challenge in critically ill and perioperative patients [1–3]. When fluid resuscitation alone fails to restore blood pressure, vasopressors represent the key intervention to correct hypotension. There are three major mechanisms to maintain blood pressure, i.e., the sympathetic nervous system, vasopressin system, and renin-angiotensin system (RAS). Each of them has the corresponding vasopressors (i.e., catecholamines, vasopressin and its derivatives, and angiotensin II) [4]. In addition, several vasoactive agents with distinct mechanisms of action (e.g., methylene blue and hydroxocobalamin) can also be used to restore blood pressure [5, 6].

Noradrenaline is recommended as the first-line vasopressor [2]; however, excessive exposure to catecholamines is associated with poor prognosis [7]. Thus, the hypothesis has emerged that administration of non-adrenergic vasopressors may reduce the catecholamine burden and improve clinical outcomes. Consistent with this, a previous meta-analysis of randomized controlled trials (RCTs) in 2015 showed potential survival benefits of non-adrenergic agents [8]. Other meta-analyses have suggested that vasopressin and its derivatives may reduce arrhythmias in septic shock [9, 10] and that methylene blue might offer survival benefits in patients with septic shock and in those undergoing cardiac surgery [11]. Moreover, angiotensin II, which became available for clinical use in 2017, has been tested in a clinical trial primarily involving septic shock patients [12] and in two RCTs in cardiac surgical settings with promising findings [13, 14]. Finally, hydroxocobalamin was also tested in a recent RCT for septic shock [6]. Given the heterogeneity of these studies in terms of patient population, comparator, type of non-adrenergic agent, and shock severity, a dedicated analysis appears desirable to account for these between-trial differences and provide an updated assessment of the outcome impact of non-adrenergic vasopressors.

Accordingly, we performed an updated systematic review and meta-analysis. We aimed to test the hypothesis that non-adrenergic vasopressors reduce mortality in adult patients receiving vasopressor therapy for vasodilatory shock or perioperative vasoplegia. To address the heterogeneity of treatment effects across different populations and different comparators, we separately analyzed studies according to patient group (septic shock, cardiac surgery, and non-cardiac surgery) and performed subgroup analyses according to the comparator (adrenergic agents or placebo).

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Supplementary material for completed checklist) [15]. We registered this study in the PROSPERO International prospective register of systematic reviews (CRD42024505039). Our review question was built using the following PICOS (Population, Intervention, Comparison, Outcome, Study design) criteria: adult patients receiving vasopressor therapy for vasodilatory shock or perioperative vasoplegia (P); non-adrenergic vasopressors (I); adrenergic vasopressors or placebo (C); mortality at the longest follow-up available (O); RCTs (S).

Search strategy and selection criteria

Four researchers independently searched PubMed, Embase, and Cochrane Central Register of Controlled Trials to identify relevant studies from inception to January 29, 2024. The complete search strategies are presented in the Supplementary material. We included RCTs comparing non-adrenergic vasopressors with adrenergic vasopressors or placebo in adult patients receiving vasopressor therapy for vasodilatory shock or perioperative vasoplegia. Non-adrenergic vasopressors included vasopressin, terlipressin, selepressin, angiotensin II, methylene blue, and hydroxocobalamin. Exclusion criteria were non-randomized trials, quasi-randomized trials, observational studies, systematic reviews, commentaries, editorials, narrative reviews, animal studies, or conference abstracts. We also excluded studies without mortality data or enrolling pediatric patients ($\leq$15 years old). No restriction was applied to language. After removing duplicates, four investigators assessed eligibility at the title/abstract level. Then, four investigators evaluated the full text of all potentially relevant articles. In case of disagreement, the final assessment was discussed with a senior investigator.

Data collection

From eligible studies, two investigators independently extracted the following variables using a standardized data collection form: first author name, publication year, number of participating centers, patient population, number of patients in the non-adrenergic and control group, the non-adrenergic vasopressor, the comparator, baseline vasopressor dose, type of comparator drug, and outcome data.

Risk of bias assessment

The risk of bias of each included RCT was assessed independently by two investigators using the Cochrane risk-of-bias tool for randomized trials version 2 (RoB 2)

[16]. The overall certainty of the evidence was evaluated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology [17]. The GRADEpro software was used to create the GRADE evidence profile table [18].

Outcomes

The primary outcome was mortality at the longest available follow-up, given that mortality is the most frequently reported patient-important primary outcome in critical care RCTs [19]. Secondary outcomes included renal replacement therapy (RRT), days of mechanical ventilation, days of intensive care unit (ICU) stay, days of hospital stay, atrial fibrillation, vasopressor-free days at day 28, and dose of noradrenaline. Dose of noradrenaline refers to the noradrenaline equivalent dose observed at the longest follow-up available.

Statistical analysis

Initially, we categorized all the included RCTs into one of three distinct groups—septic shock, cardiac surgery, or non-cardiac surgery—based on the majority population in each study. Meta-analysis was performed separately for these three groups. Subgroup analysis was conducted according to type of non-adrenergic agents (vasopressin, terlipressin, selepressin, angiotensin II, methylene blue, and hydroxocobalamin), comparator (placebo and adrenergic agents), baseline vasopressor dose (above or below the median value in septic shock), exclusion of studies assessing nitric oxide scavengers (methylene blue and hydroxocobalamin), and studies with overall low risk of bias. We also performed the following sensitivity analyses for the primary outcome: timing of assessment (< 28 days, 28 or 30 days, and > 30 days), exclusion of a study using dopamine as control treatment, exclusion of studies using selepressin as the intervention, timing of administration (first-line versus second- or third-line therapy), studies published in high-impact journals [20, 21] (the complete journal selection is detailed in the Table S1), and studies published before versus after 2014.

Throughout this study, we calculated individual and pooled effects estimate (risk ratio [RR] for binary variables and mean difference [MD] or standardized mean difference [SMD] for continuous variables) with 95% confidence interval (CI) using a Mantel–Haenszel random-effects model for all the outcomes assuming heterogeneity of treatment effects due to clinical heterogeneity among studies. Statistical heterogeneity was assessed using the I^2 statistics, and publication bias was evaluated by visual inspection of funnel plots. We used Review Manager 5.4 and considered two-sided p values < 0.05 statistically significant.

To assess the possible effect modification for mortality by baseline vasopressor dose, we performed a meta-regression analysis using a mixed-effects model. A noradrenaline equivalent score was used to calculate the total vasopressor dose [22]. The analysis was performed using R 4.0.1.

Trial sequential analysis (TSA) was performed to investigate the robustness of the pooled primary outcome data [23]. We used the weighted mortality data in the control group and anticipated a 10% relative risk reduction when non-adrenergic vasopressors are applied, with a diversity-adjusted information size calculated using a two-sided alpha of 0.05 and a power of 80%. The TSA Viewer software was used (Version 0.9.5.10 Beta. Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark).

Results

From 6159 records identified through literature search, we included 51 RCTs with a total of 5715 patients (Table 1 and Fig. 1) [5, 6, 12–14, 24–69]. The major exclusions and reasons for exclusion are shown in Table S2. The predominant population investigated was septic shock in 30 studies [5, 6, 12, 24–50], cardiac surgery in 11 studies [13, 14, 51–59], and non-cardiac surgery in 10 studies [60–69]. The non-adrenergic agent assessed was vasopressin in 16 studies [26, 29–32, 34, 37, 39, 45, 52, 54, 56, 57, 59, 61, 68], terlipressin in 15 studies [24, 25, 28, 33, 38, 42, 46, 48–50, 62, 65–67, 69], selepressin in two studies [36, 44], angiotensin II in five studies [12–14, 27, 51], methylene blue in 11 studies [5, 35, 40, 41, 47, 53, 55, 58, 60, 63, 64], and hydroxocobalamin in one study [5, 6, 12, 13, 25, 33, 34, 37, 39, 42, 45, 51, 53–58, 60–65, 67]. The remaining study randomized patients into three groups (vasopressin, terlipressin, or noradrenaline) and was categorized as a vasopressin study in subgroup analyses based on drug type [43].

Placebo was used as a comparator in 25 studies [5, 6, 12, 13, 27, 35, 36, 39, 41, 44, 47, 53, 55–60, 62–67, 69], while adrenergic agents were administered and served as comparator in 26 studies [14, 24–26, 28–34, 37, 38, 40, 42, 43, 45, 46, 48–52, 54, 61, 68]. The baseline noradrenaline equivalent dose was 0.28 μg/kg/min in septic shock [5, 6, 12, 24, 25, 29, 31, 33, 37–39, 41, 43–46, 49] and 0.20 μg/kg/min in cardiac surgery [14, 53–56, 58, 59], while no patient received vasopressors at baseline in non-cardiac surgery settings [60, 61, 63, 65, 68, 69]. The characteristics of the included studies and noradrenaline products used are summarized in Table 1 and Table S3.

The risk of bias assessment using RoB 2 deemed 17 studies as being at low risk of bias [5, 12–14, 27, 31, 32, 36, 38, 44, 45, 52, 60, 61, 63, 66, 67], 16 studies as having some concerns [6, 24, 28, 29, 35, 37, 41, 43, 48, 49, 51, 55,

Table 1 Characteristics of the included studies

First author, year	No. of centers	Country	No. of patients	Baseline noradrenaline equivalent dose, μg/kg/min	Dose of non-adrenergic agents	Comparator	Follow-up
Septic shock							
Vasopressin							
Malay MB, 1999 [39]	1	USA	10	0.33	0.04 U/min	Placebo	24 h
Dunser MW, 2003 [29]	1	Austria	48	0.84	4 U/h	Noradrenaline	ICU stay
Lauzier F, 2006 [37]	2	Multinational	23	0.27	0.04–0.2 U/min	Noradrenaline	48 h
Russell JA, 2008 [45]	27	Multinational	778	0.25	0.01–0.03 U/min	Noradrenaline	90 days
Fonseca-Ruiz NJ, 2013 [30]	1	Colombia	30	NR	0.01–0.04 U/min	Noradrenaline	28 days
Barzegar E, 2014 [26]	1	Iran	30	NR	0.03 U/min	Noradrenaline	28 days
Gordon A, 2016 [31]	18	England	408	0.18	0.06 U/min	Noradrenaline	28 days
Hajjar LA, 2019 [32]	1	Brazil	250	0	0.01–0.06 U/min	Noradrenaline	90 days
Hussien RM, 2021 [34]	1	Egypt	90	NR	0.03 U/min	Noradrenaline	28 days
Terlipressin							
Albanese J, 2005 [24]	1	France	20	0	1 mg bolus	Noradrenaline	Hospital stay
Morelli A, 2008 [42]	1	Italy	39	NR	1 mg bolus	Noradrenaline	ICU stay
Svoboda P, 2012 [48]	1	Czech Republic	30	NR	4 mg/24 h for 72h	Noradrenaline	90 days
Hua F, 2013 [33]	1	China	32	0	1.3 mg/kg/h for 48 h	Dopamine	28 days
Choudhury A, 2016 [28]	1	India	84	NR	1.3–5.2 μg/min	Noradrenaline	28 days
Xiao X, 2016 [50]	1	China	32	NR	1.3 mg/kg/h	Noradrenaline	7 days
Liu ZM, 2018 [38]	21	China	526	0.55	20–160 μg/h	Noradrenaline	28 days
Arora V, 2020 [25]	1	India	120	NR	2–12 mg/24 h	Noradrenaline	28 days
Sahoo P, 2022 [46]	1	India	50	0.22	0.02 mg/kg/min	Noradrenaline	ICU stay
Wang J, 2022 [49]	1	China	22	0.29	1.3 mg/kg/h for 24 h	Noradrenaline	28 days
Vasopressin & Terlipressin (3 arms)							
Morelli A 2009 [43]	1	Italy	45	0	Vasopressin: 0.03 U/min Terlipressin: 1.3 μg/kg/min for 48 h	Noradrenaline	ICU stay
Selepressin							
Russell JA, 2017 [44]	NR	Multinational	50	0.28	1.25–3.75 ng/kg/min	Placebo	28 days
Laterre PF, 2019 [36][c]	63	Multinational	828	0.28	1.7–5 ng/kg/min	Placebo	90 days
Angiotensin II							
Chawla LS, 2014 [27]	1	USA	20	NR	20 ng/kg/min	Placebo	30 days
Khanna A, 2017 [34]	75	Multinational	321	0.37	40 ng/kg/min	Placebo	28 days
Methylene blue							
Kirov MY, 2001 [35]	1	Russia	20	NR	2 mg/kg bolus + 0.25–2 mg/kg/h for 2 h	Placebo	28 days
Memis D, 2002 [41]	1	Turkey	30	0	0.5 mg/kg/h for 6 h	Placebo	Hospital stay
Senthilnathan M, 2017 [47]	1	India	30	NR	2 mg/kg	Placebo	7 days
Lu YP, 2019 [40]	1	China	54	NR	2 mg/kg	Noradrenaline	28 days
Ibarra Estrada M, 2023 [56]	1	Mexico	92	0.41	1.2 mg/kg/day	Placebo	28 days
Hydroxocobalamin							
Patel JJ, 2023 [52]	2	Multinational	20	0.32	5 g	Placebo	Hospital stay

Table 1 (continued)

First author, year	No. of centers	Country	No. of patients	Baseline noradrenaline equivalent dose, μg/kg/min	Dose of non-adrenergic agents	Comparator	Follow-up
Cardiac surgery							
Vasopressin							
Morales DLS, 2003 [56]	1	USA	27	0	0.03 U/min for 72 h	Placebo	ICU stay
Luckner G, 2006 [54]	1	Austria	18	0.70	4 U/h	Noradrenaline	ICU stay
Papadopoulos G, 2010 [59]	1	Greece	50	0	0.03 U/min	Placebo	48 h
Okamoto Y, 2014 [57]	1	Japan	92	NR	1.8 U/min	Placebo	30 days
Hajjar LA, 2017 [52]	1	Brazil	300	NR	0.01–0.06 U/min	Noradrenaline	90 days
Angiotensin II							
Bennett SR, 2001 [51]	1	UK	20	NR	NR	Phenylephrine	48 h
Coulson TG, 2022 [65]	2	Australia	60	0	1–40 ng/kg/min	Noradrenaline	Hospital stay
Sadjadi M, 2024 [59]	1	Germany	63	NR	20–80 ng/kg/min	Placebo	90 days
Methylene blue							
Levin RL, 2004 [53]	4	Argentina	56	0.71	1.5 mg/kg for 1 h	Placebo	Hospital stay
Ozal E, 2005 [58]	1	Turkey	100	0	2 mg/kg	Placebo	Hospital stay
Maslow AD, 2006 [55]	1	America	30	0	3 mg/kg	Placebo	ICU stay
Non-cardiac surgery							
Vasopressin							
Song T, 2015 [68]	1	Korea	60	0	0.2–1 U/min	Epinephrine	Hospital stay
Elgebaly AS, 2019 [61]	1	Egypt	30	0	0.1–0.4 U/min	Noradrenaline	28 days
Terlipressin							
Hong SH, 2012 [62]	1	Chorea	41	NR	1–4 μg/kg/h	Placebo	10 days
Reddy MS, 2017 [67]	1	India	41	NR	1 mg + 2 μg/kg/h for 72 h	Placebo	30 days
Mahdy MM, 2019 [66]	1	Egypt	50	NR	1 mg bolus + 2 μg/kg/h	Placebo	Hospital stay
Kohler A, 2020 [65]	1	Switzerland	130	0	1 mg	Placebo	6 weeks
Zhang L, 2023 [69]	1	China	64	0	1 mg	Placebo	Hospital stay
Methylene blue							
Koelzow H, 2002 [64]	1	England	38	NR	1.5 mg/kg	Placebo	30 days
Deng Y, 2021 [60]	1	China	248	0	2 mg/kg	Placebo	3 months
Huang J, 2022 [63]	1	China	70	0	2 mg/kg	Placebo	6 months

ICU, intensive care unit; NR, not reported; UK, United Kingdom; USA, United States of America

57, 58, 62, 68, 69], and 18 studies as being at high risk of bias [25, 26, 30, 33, 34, 39, 40, 42, 46, 47, 50, 53, 54, 56, 59, 64, 65, 70] (Table S4).

Primary outcome

In septic shock studies (30 RCTs with 4122 patients), the administration of non-adrenergic vasopressors was associated with a significantly reduced mortality (RR, 0.92; 95% CI, 0.86 to 0.97; $P=0.03$; $I^2=0\%$) (Table 2 and Fig. 2). The primary outcome data were similar in the sensitivity analyses except for the one addressing hydroxocobalamin (Fig. 2A and Fig. S1). The TSA confirmed the robustness of evidence indicating reduced mortality with the use of non-adrenergic agents (Fig. S2).

No significant mortality differences were observed in 11 cardiac surgery studies with 822 patients (34/410 [8.3%] vs. 47/412 [11%]; RR, 0.82; 95% CI, 0.55 to 1.22; $P=0.32$; $I^2=12\%$) and in 10 non-cardiac surgery studies with 771 patients (9/388 [2.3%] vs. 18/383 [4.7%]; RR, 0.66; 95% CI, 0.31 to 1.44; $P=0.28$; $I^2=24\%$) (Table 2,

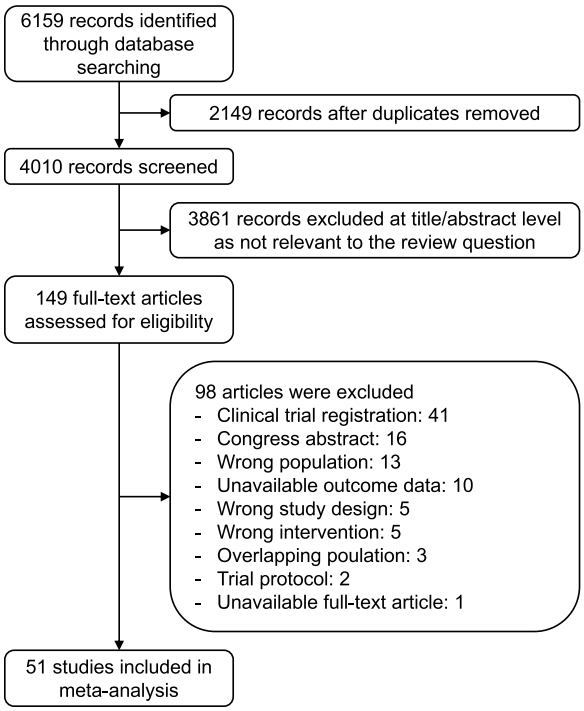
6159 records identified through database searching
2149 records after duplicates removed
4010 records screened
3861 records excluded at title/abstract level as not relevant to the review question
149 full-text articles assessed for eligibility
98 articles were excluded
- Clinical trial registration: 41
- Congress abstract: 16
- Wrong population: 13
- Unavailable outcome data: 10
- Wrong study design: 5
- Wrong intervention: 5
- Overlapping poulation: 3
- Trial protocol: 2
- Unavailable full-text article: 1
51 studies included in meta-analysis

Fig. 1 Flow chart of study selection

Fig. 2B and C). Sensitivity analyses focused on studies with low risk of bias were consistent with the main analyses (Figs. S3–S4). The TSA for cardiac and non-cardiac surgery settings showed the need for further RCTs to draw a definitive conclusion (required sample size, 40,151 and 60,626, respectively). Visual inspection of the funnel plot suggested potential small-study effects in all the three settings (Figs. S5–S7). The timeframe to observe mortality at the longest follow-up is summarized in Table S5a. A sensitivity analysis based on the timeframe yielded similar findings with the main analysis (Table S5b). Results of the other sensitivity analyses for mortality are summarized in Table S6. These sensitivity analyses did not materially change our findings.

The effect modification by baseline vasopressor dose on mortality was explored in septic shock studies. 20 studies contributed baseline vasopressor doses, and meta-regression analysis showed no evident change in the mortality risk ratio for a change in baseline vasopressor dose (Estimate 0.21 [95%CI, −0.15 to 0.58], tau = 0.05, $I^2 = 10.1\%$, Fig. S8). As we applied continuity correction to one study in the septic shock studies, we performed additional analysis excluding the trial, which did not change the findings. For cardiac surgery studies, only seven studies reported baseline vasopressor doses, six of which reported zero death in either or both groups. Given such data do not provide reliable effect estimates, we did not perform meta-regression analysis in this population. None of the non-cardiac surgery studies reported baseline vasopressor doses.

Secondary outcomes

Septic shock

The administration of non-adrenergic agents was associated with reduced risk of RRT (9 studies; RR, 0.68; 95% CI, 0.57 to 0.81; $I^2 = 0\%$), reduced days of mechanical ventilation (7 studies; MD, −0.73 days; 95% CI, −1.15 to −0.31; $I^2 = 0\%$), reduced risk of atrial fibrillation (16 studies; RR, 0.65; 95% CI, 0.43 to 0.98; $I^2 = 36\%$), increased vasopressor-free days (8 studies; MD, 1.28; 95% CI, 0.54 to 2.03; $I^2 = 25\%$), and reduced dose of noradrenaline (10 studies; SMD, −1.17; 95% CI, −1.75 to −0.59; $I^2 = 93\%$). No detectable differences were observed in days of ICU stay or days of hospital stay (Table 3, Figs. S9–S15).

Cardiac surgery

Non-adrenergic vasopressors were associated with reduced risk of RRT (4 studies; RR, 0.19; 95% CI, 0.07 to 0.48; $I^2 = 0\%$), shortened days of ICU stay (6 studies; MD, −0.66 days; 95% CI, −1.22 to −0.11; $I^2 = 73\%$), shortened days of hospital stay (4 studies; MD, −1.83 days; 95% CI, −3.57 to −0.09; $I^2 = 86\%$), reduced risk of atrial fibrillation (6 studies; RR, 0.76; 95% CI, 0.67 to 0.87; $I^2 = 0\%$), increased vasopressor-free days (3 studies; MD, 0.29; 95% CI, 0.16 to 0.42; $I^2 = 0\%$), and reduced dose of noradrenaline (4 studies; SMD, −2.24; 95% CI, −3.90 to −0.59; $I^2 = 95\%$). No significant difference was observed in days of mechanical ventilation (Table 4, Figs. S16–S22).

Non-cardiac surgery

Among secondary outcomes, non-adrenergic vasopressors were associated with shortened ICU stay (4 studies; MD, −0.72 days; 95% CI, −1.19 to −0.24; $I^2 = 15\%$) and reduced dose of noradrenaline (4 studies; SMD, −1.16; 95% CI, −2.05 to −0.28; $I^2 = 89\%$), while other outcomes were not different (Table 5, Figs. S23–S28).

The GRADE evaluation is shown in Table S7. Results of sensitivity analyses based on control treatment (placebo vs. adrenergic vasopressors) and baseline vasopressor dose (high vs. low) are summarized in Tables S8 and S9. These sensitivity analyses aligned with the main analysis.

Discussion

Key findings

In this systematic review and meta-analysis of 51 RCTs, we evaluated the effects of non-adrenergic vasopressors on clinical outcomes in three distinct populations. The use of non-adrenergic agents was associated with a reduced mortality risk in patients with septic shock. It was also associated with reduced RRT use and

Table 2 Effects of non-adrenergic vasopressor administration on mortality

Group	No. of studies	Non-adrenergic agents	Control	Risk ratio (95% CI)	*P* value	I^2
Septic shock	30	960/2232 (43%)	898/1890 (48%)	0.92 (0.86 to 0.97)	0.03	0%
Vasopressin	10	378/867 (44%)	392/838 (47%)	0.93 (0.85 to 1.02)	0.14	0%
Terlipressin	10	222/470 (47%)	254/485 (52%)	0.89 (0.77 to 1.02)	0.10	32%
Selepressin	2	247/591 (42%)	120/285 (42%)	0.98 (0.83 to 1.16)	0.84	0%
Angiotensin II	2	80/173 (46%)	91/168 (54%)	0.85 (0.69 to 1.06)	0.14	0%
Methylene blue	5	29/121 (24%)	37/104 (36%)	0.72 (0.49 to 1.04)	0.08	0%
Hydroxocobalamin	1	4/10 (40%)	4/10 (40%)	1.00 (0.34 to 2.93)	0.99	NA
Placebo as comparator	10	355/864 (41%)	249/554 (45%)	0.91 (0.81 to 1.03)	0.14	0%
Adrenergic agents as comparator	20	927/2101 (44%)	649/1336 (49%)	0.92 (0.86 to 0.98)	0.01	0%
Exclusion of studies assessing nitric oxide scavengers	24	927/2101 (44%)	857/1776 (48%)	0.92 (0.87 to 0.98)	0.008	0%
Low risk of bias studies	9	771/1790 (43%)	671/1473 (46%)	0.95 (0.88 to 1.02)	0.14	0%
Cardiac surgery	11	34/410 (8.3%)	47/412 (11%)	0.82 (0.55 to 1.22)	0.32	12%
Vasopressin	5	32/248 (13%)	37/245 (15%)	0.89 (0.65 to 1.22)	0.48	0%
Angiotensin II	3	2/69 (2.9%)	2/74 (2.7%)	0.98 (0.15 to 6.38)	0.99	0%
Methylene blue	3	0/93 (0%)	8/93 (8.6%)	0.12 (0.02 to 0.95)	0.04	0%
Placebo as comparator	7	1/213 (0.5%)	14/211 (6.6%)	0.22 (0.06 to 0.77)	0.02	0%
Adrenergic agents as comparator	4	33/197 (17%)	33/201 (16%)	0.93 (0.68 to 1.28)	0.67	0%
Exclusion of studies assessing nitric oxide scavengers	8	34/317 (11%)	39/319 (12%)	0.90 (0.66 to 1.22)	0.48	0%
Low risk of bias studies	3	25/208 (12%)	28/215 (13%)	0.91 (0.56 to 1.49)	0.71	0%
Non-cardiac surgery	10	9/388 (2.3%)	18/383 (4.7%)	0.66 (0.31 to 1.41)	0.28	0%
Vasopressin	2	0/45 (0%)	5/45 (11%)	0.09 (0.01 to 1.51)	0.09	NA
Terlipressin	5	1/164 (0.6%)	5/161 (3.1%)	0.34 (0.07 to 1.71)	0.19	0%
Methylene blue	3	8/179 (4.5%)	8/177 (4.5%)	1.00 (0.40 to 2.48)	0.99	0%
Placebo as comparator	8	9/343 (2.6%)	13/338 (3.8%)	0.77 (0.35 to 1.70)	0.52	0%
Adrenergic agents as comparator	2	0/45 (0%)	5/45 (11%)	0.09 (0.01 to 1.51)	0.09	NA
Exclusion of studies assessing nitric oxide scavengers	7	1/209 (0.5%)	10/206 (4.9%)	0.25 (0.06 to 0.998)	0.0497	0%
Low risk of bias studies	5	3/220 (1.4%)	11/219 (5.0%)	0.44 (0.15 to 1.34)	0.15	0%

Abbreviations: CI = confidence interval; NA = not applicable

occurrence of atrial fibrillation both in patients with septic shock and in those undergoing cardiac surgery. Moreover, we observed shortened ICU and hospital stays in cardiac surgery settings. Finally, noradrenaline dose was decreased across all three settings.

Relationship with previous literature

To our knowledge, this systematic review is the most updated and comprehensive evaluation of the efficacy of non-adrenergic vasopressors in various etiologies. Unlike previous meta-analyses confined to specific vasopressors (vasopressin and its analogues [9, 10, 71–73], angiotensin II [74], or methylene blue [11, 75]) and specific populations (septic shock [71, 74, 75], septic shock and cardiac surgery [69, 70], cardiac surgery [72], or any surgery [73]), our review included all non-adrenergic agents available in three different settings (septic shock, cardiac surgery, and non-cardiac surgery). This inclusive approach increased the number of studies and sample size, while maintaining separate analyses according to study populations to take into account the heterogeneity of treatment effects in different settings.

Mortality

In patients with septic shock, we observed a mortality reduction, which was mainly driven by vasopressin and methylene blue. This finding aligns with previous meta-analyses [9, 11, 71, 75]. However, it should be noted that such significant mortality reduction was not confirmed when each non-adrenergic agent was analyzed separately. On the other hand, in cardiac and non-cardiac settings, similar to previous meta-analyses in surgical settings [72, 73], mortality differences did not reach statistical significance. Nevertheless, the overall analysis and the vast majority of sensitivity analyses across three different populations found a pooled RR < 1 for mortality.

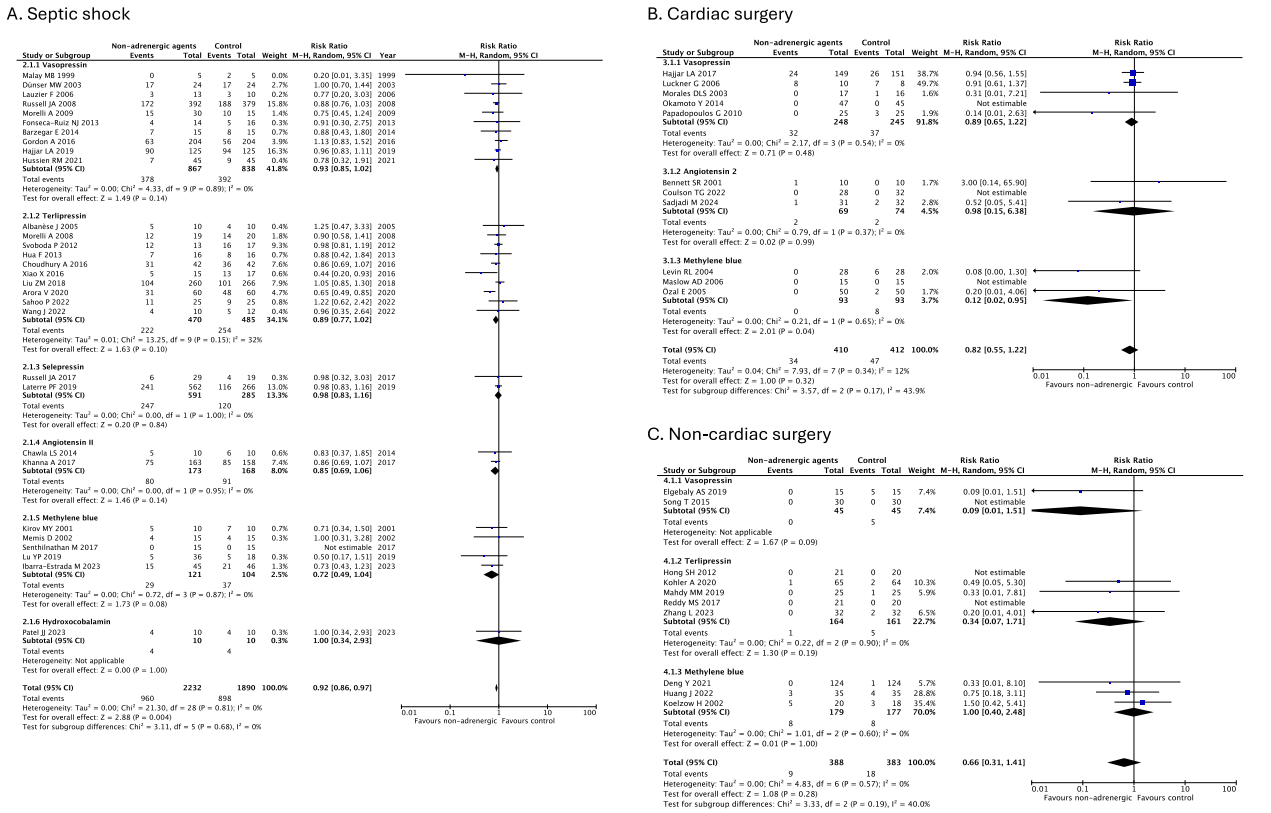

Fig. 2 Forest plot for mortality. **A** Septic shock. **B** Cardiac surgery. **C** Non-cardiac surgery

Secondary outcomes

Use of renal replacement therapy was significantly reduced in septic shock and in cardiac surgery, with a similar point estimate in non-cardiac surgery settings. Such benefits were mainly driven by vasopressin and angiotensin II. The renal protection associated with vasopressin was consistent with a previous meta-analysis [76] and has been attributed to preferential post-glomerular vasoconstriction [76]. Angiotensin II seems to exert its renoprotective effects through its specific vasoconstrictive effects on efferent arterioles, since dilatation of efferent arterioles is a key pathological finding of sepsis-associated AKI. Indeed, angiotensin II therapy might confer survival benefits in refractory vasodilatory shock patients on RRT [77].

Duration of mechanical ventilation, ICU stay, and hospital stay appeared shortened with non-adrenergic vasopressor administration. Given the increased vasopressor-free days and reduced noradrenaline dose, it is plausible to think that adding a vasopressor with distinct mechanisms of action could restore blood pressure successfully while avoiding some of the complications related to adrenergic vasopressors or preventing excessive fluid administration. These assumptions are supported by the reduction of atrial fibrillation.

Implications for clinical practice and future research

Our meta-analysis implies that the administration of non-adrenergic vasopressors may reduce mortality in patients with septic shock. Since the annual sepsis-related deaths are estimated to be 11 million worldwide [78], the relative risk reduction of 0.08 would potentially translate into hundreds of thousands of lives saved every year. Moreover, avoidance of RRT and facilitated liberation from mechanical ventilation would not only prevent various complications attributable to such interventions but also save considerable healthcare resources and potentially improve long-term health-related quality of life.

Another important implication is that non-adrenergic vasopressors may reduce arrhythmia risks and noradrenaline dosage across different settings. This observation suggests hemodynamic safety and efficacy for non-adrenergic vasopressor strategy. Moreover, such observations were consistent irrespective of drug type or comparator.

From a research perspective, our meta-analysis implies that phase III clinical trials dedicated to each agent and setting are warranted to draw a definitive answer. Moreover, precision approach is highly needed to identify which patient subgroups would most benefit

Table 3 Effects of non-adrenergic agents on secondary outcomes in septic shock settings

Secondary outcome	No. of studies	Non-adrenergic agents	Control	Risk ratio (95% CI)	Mean difference/ standardized mean difference (95% CI)	*P* value	I^2
Renal replacement therapy	9	115/528 (22%)	170/509 (29%)	0.68 (0.57 to 0.81)		< 0.0001	0%
Vasopressin	6	77/433 (18%)	112/414 (27%)	0.66 (0.51 to 0.84)		0.0009	0%
Terlipressin	2	35/85 (41%)	54/85 (64%)	0.48 (0.12 to 1.84)		0.28	54%
Hydroxocobalamin	1	3/10 (30%)	4/10 (40%)	0.75 (0.22 to 2.52)		0.64	NA
Days of mechanical ventilation	7				− 0.73 (− 1.15 to − 0.31)	0.0006	0%
Vasopressin	1				− 1.00 (− 2.39 to 0.39)	0.16	NA
Terlipressin	2				− 1.00 (− 1.97 to − 0.03)	0.04	0%
Selepressin	1				− 0.20 (− 1.39 to 0.99)	0.74	NA
Methylene blue	3				− 0.72 (− 1.26 to − 0.17)	0.01	0%
Days of ICU stay	14				− 0.69 (− 1.49 to 0.12)	0.10	52%
Vasopressin	6				− 0.31 (− 2.08 to 1.47)	0.74	75%
Terlipressin	4				− 0.01 (− 1.12 to 1.11)	0.99	0%
Selepressin	1				− 0.70 (− 2.02 to 0.62)	0.30	NA
Methylene blue	3				− 1.62 (− 2.95 to − 0.30)	0.02	19%
Days of hospital stay	6				− 0.73 (− 3.42 to 1.96)	0.60	64%
Vasopressin	4				− 2.24 (− 5.69 to 1.20)	0.20	64%
Terlipressin	2				2.19 (− 0.29 to 4.67)	0.08	0%
Atrial fibrillation	16	82/813 (10%)	120/794 (15%)	0.65 (0.43 to 0.98)		0.04	36%
Vasopressin	8	45/461 (10%)	78/449 (17%)	0.40 (0.19 to 0.83)		0.01	55%
Terlipressin	5	13/150 (8.7%)	20/156 (13%)	0.80 (0.33 to 1.96)		0.63	27%
Selepressin	1	0/29 (0%)	1/21 (4.8%)	0.24 (0.01 to 5.72)		0.38	NA
Angiotensin II	2	24/173 (14%)	21/168 (13%)	1.16 (0.49 to 2.77)		0.74	10%
Vasopressor-free days at day 28	8				1.28 (0.54 to 2.03)	0.0007	25%
Vasopressin	1				0.70 (− 1.81 to 3.21)	0.55	NA
Terlipressin	3				1.93 (1.43 to 2.43)	< 0.0001	0%
Selepressin	1				− 0.40 (− 2.19 to 1.39)	0.66	NA
Methylene blue	2				0.94 (− 0.60 to 2.47)	0.23	0%
Hydroxocobalamin	1				− 1.40 (− 20.95 to 18.15)	0.89	NA
Dose of noradrenaline*	10				− 1.17 (− 1.75 to − 0.59)	< 0.0001	93%
Vasopressin	4				− 1.29 (− 1.82 to − 0.76)	< 0.0001	60%
Terlipressin	3				− 2.27 (− 6.63 to 2.08)	0.31	98%
Angiotensin II	2				− 0.39 (− 1.22 to 0.43)	0.35	69%
Hydroxocobalamin	1				− 0.65 (− 1.55 to 0.26)	0.16	NA

* Indicates that the treatment effect is expressed with a standardized mean difference and 95% confidence interval

ICU, intensive care unit; NA, not applicable

from a non-adrenergic vasopressor [79]. For example, hyperreninemia might identify patients in whom angiotensin II might increase the chance of survival [80]. Such personalized vasopressor therapy, rather than a one-size-fits-all strategy, should also be evaluated in future RCTs. Furthermore, cost-effectiveness analysis would help decision making in countries where non-adrenergic agents are considered too expensive or in resource-limited settings.

Strengths and limitations

The strengths of this meta-analysis include the pre-registered protocol, a statistical analysis which accounted for clinical heterogeneity, and comprehensive approach

Table 4 Effects of non-adrenergic agents on secondary outcomes in cardiac surgery settings

Secondary outcome	No. of studies	Non-adrenergic agents	Control	Risk ratio (95% CI)	Mean difference/ standardized mean difference (95% CI)	*P* value	I^2
Renal replacement therapy	4	4/236 (1.7%)	26/243 (11%)	0.19 (0.07 to 0.48)		0.0005	0%
Vasopressin	1	4/149 (2.7%)	21/151 (14%)	0.19 (0.07 to 0.55)		0.002	NA
Angiotensin II	2	0/59 (0%)	3/64 (4.7%)	0.16 (0.01 to 3.02)		0.22	NA
Methylene blue	1	0/28 (0%)	2/28 (7.1%)	0.20 (0.01 to 3.99)		0.29	NA
Days of mechanical ventilation (vasopressin only)	2				−0.12 (−0.61 to 0.36)	0.62	86%
Days of ICU stay	6				−0.66 (−1.22 to −0.11)	0.02	73%
Vasopressin	3				−0.50 (−1.41 to 0.41)	0.28	83%
Angiotensin II	2				−1.04 (−2.00 to −0.07)	0.03	0%
Methylene blue	1				−0.90 (−1.26 to −0.54)	< 0.0001	NA
Days of hospital stay	4				−1.83 (−3.57 to −0.09)	0.04	86%
Vasopressin	2				−2.30 (−6.22 to 1.62)	0.25	95%
Angiotensin II	1				0.20 (−2.30 to 2.70)	0.88	NA
Methylene blue	1				−2.30 (−3.03 to −1.57)	< 0.0001	NA
Atrial fibrillation	6	125/292 (43%)	169/295 (57%)	0.76 (0.67 to 0.87)		< 0.0001	0%
Vasopressin	1	112/190 (59%)	148/188 (78%)	0.76 (0.67 to 0.87)		< 0.0001	0%
Angiotensin II	2	6/59 (10%)	8/64 (13%)	0.90 (0.36 to 2.26)		0.82	0%
Methylene blue	1	7/43 (16%)	13/43 (30%)	0.55 (0.14 to 2.21)		0.40	60%
Vasopressor-free days at day 28	3				0.29 (0.16 to 0.42)	< 0.0001	0%
Vasopressin	2				0.28 (0.15 to 0.41)	< 0.0001	0%
Angiotensin II	1				1.00 (−0.34 to 2.34)	0.14	NA
Dose of noradrenaline* (vasopressin only)	4				−2.24 (−3.90 to −0.59)	0.008	95%

* Indicates that the treatment effect is expressed with a standardized mean difference and 95% confidence interval

ICU, intensive care unit; NA, not applicable

regarding non-adrenergic vasopressor types and clinical indications.

We acknowledge several limitations. First, we aggregated data of studies using different non-adrenergic agents and comparators. Furthermore, there was considerable heterogeneity in the way non-adrenergic agents were initiated, titrated, weaned, and terminated among the included studies. However, we performed sensitivity analyses to evaluate their impacts on the effect size. Moreover, it was reassuring that none of the sensitivity analyses found an increased mortality risk in the non-adrenergic vasopressor group. Second, mortality was reported at different time points. As a previous work showed that this approach does not affect the overall treatment effects in critical care settings [81], we synthesized mortality data at different time points. Moreover, a sensitivity analysis based on the timing found consistent results with the main analysis. Third, only one-third of the included studies were judged to be at low risk of bias or published in well-recognized journals. As a result, sensitivity analyses focused on such high-quality studies or studies published in high-impact journals did not find a statistically significant mortality reduction in any setting assessed. Nonetheless, the point estimates were similar to the overall results, suggesting potential positive effects on survival. Fourth, there is intense debate on whether nitric oxide scavengers are considered vasopressors or not. However, these agents have gained growing attention as a rescue therapy in refractory vasodilatory shock. Furthermore, sensitivity analyses assessing these agents separately or excluding them confirmed the findings of the main analysis, suggesting that our findings are likely robust. Fifth, standard of care outside use of vasopressors was not always well-defined. However, thanks to the randomized design, it seems plausible to assume that both groups were balanced regarding care outside the intervention of interest and that this limitation had little influence on the estimated effects. Sixth, the publication year of the included studies spanned 25 years. Complete data extraction was not always feasible in old studies. Standard intensive care may change over time. However, a sensitivity analysis according to the publication year

Table 5 Effects of non-adrenergic agents on secondary outcomes in non-cardiac surgery settings

Secondary outcome	No. of studies	Non-adrenergic agents	Control	Risk ratio (95% CI)	Mean difference/ standardized mean difference (95% CI)	*P* value	I^2
Renal replacement therapy	3	2/83 (2.4%)	3/82 (3.7%)	0.74 (0.15 to 3.74)		0.71	0%
Vasopressin	1	0/30 (0%)	0/30 (14%)	Not estimable		NA	NA
Terlipressin	2	2/53 (3.8%)	3/52 (5.8%)	0.74 (0.15 to 3.74)		0.71	0%
Days of mechanical ventilation (terlipressin only)	3				−0.26 (−1.72 to 1.19)	0.72	74%
Days of ICU stay	4				−0.72 (−1.19 to −0.24)	0.003	15%
Terlipressin	3				−0.56 (−1.29 to 0.17)	0.14	34%
Methylene blue	1				−0.90 (−1.53 to −0.27)	0.005	NA
Days of hospital stay	4				−0.71 (−2.28 to 0.87)	0.38	35%
Vasopressin	1				−0.30 (−1.30 to 0.70)	0.59	NA
Terlipressin	2				−1.41 (−5.25 to 2.43)	0.47	59%
Methylene blue	1				0.70 (−3.56 to 4.96)	0.75	NA
Atrial fibrillation	4	5/240 (2.1%)	8/238 (3.4%)	0.65 (0.13 to 3.32)		0.61	38%
Vasopressin	1	0/30 (0%)	0/30 (14%)	Not estimable		NA	NA
Terlipressin	2	5/86 (5.8%)	4/84 (4.8%)	1.22 (0.32 to 4.70)		0.78	0%
Methylene blue	1	0/30 (0%)	0/30 (14%)	0.11 (0.01 to 2.04)		0.14	NA
Dose of noradrenaline*	3				−1.38 (−2.67 to −0.09)	0.04	93%
Terlipressin	1				−0.46 (−0.96 to 0.04)	0.07	NA
Methylene blue	2				−1.94 (−4.65 to 0.77)	0.16	96%

* Indicates that the treatment effect is expressed with a standardized mean difference and 95% confidence interval

ICU, intensive care unit; NA, not applicable

did not find heterogeneity in effects on mortality. Finally, most studies failed to clarify which noradrenaline formulation was used and whether they reported the dose of noradrenaline base, which could result in inconsistent dosage comparison. Future trials should use a uniform dose reporting with noradrenaline base [82].

Conclusions

Use of non-adrenergic vasopressors was associated with a mortality reduction in patients with septic shock, though subgroup analyses of individual non-adrenergic vasopressors did not show a significant survival benefit. No significant mortality difference was observed in cardiac or non-cardiac surgery settings. Moreover, in both septic shock and cardiac surgery patients, non-adrenergic agents were associated with reduced RRT use and less atrial fibrillation both in patients with septic shock and in those undergoing cardiac surgery. Finally, across all three settings, noradrenaline dose was decreased. These findings justify the conduct of phase III trials comparing these agents to usual care based on noradrenaline alone.

Abbreviations

CI Confidence interval
ICU Intensive care unit
PRISMA Preferred reporting items for systematic reviews and meta-analyses
RCT Randomized controlled trial
RR Relative risk
TSA Trial sequential analysis

Supplementary Information

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Supplementary Material 1.

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Author contributions

YK, ABe, FD, ABo, PMW, TF, AKK, GL, and RB conceived the study. YK, ABe, FD, ABo, and GL designed the search strategy and did the literature search. YK, ABo, TF, and GL did the statistical analysis. YK, ABe, FD, PMW, TF, AKK, GL, and RB wrote the initial protocol. YK wrote the initial manuscript draft. All authors shared the study data, gave a critical appraisal of the protocol, provided crucial revisions, and approved the final manuscript.

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Availability of data and materials

We collected the summary data from published randomized trials. This published article and its supplementary files include all the data generated or analyzed for this study. Further information is available from the corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
YK has received consultancy fees from Viatris. PMW previously received consultant fees from Viatris. AKK received consulting fees from Medtronic, Edwards Life Sciences, Philips Research North America, Hillrom, GE Healthcare, Potrero Medical, Viatris Pharma, Trevena Pharma, Fifth Eye Inc., Pharmazz Inc., Retia Medical and Caretaker Medical. He is also funded with a Wake Forest Clinical and Translational Science Institute (CTSI) grant on renin dysfunction in septic shock. GL has received speaker fees from Medis, Paion, and Viatris and consultancy fees from Paion and Viatris. RB has received grants and consultancy fees from La Jolla Pharmaceuticals, Paion AG, and Viatris. The other authors have no competing interests.

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References
1. Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013;369:1726–34.
2. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47:1181–247.
3. Busse LW, Barker N, Petersen C. Vasoplegic syndrome following cardiothoracic surgery-review of pathophysiology and update of treatment options. Crit Care. 2020;24:36.
4. Leone M, Einav S, Antonucci E, Depret F, Lakbar I, Martin-Loeches I, et al. Multimodal strategy to counteract vasodilation in septic shock. Anaesth Crit Care Pain Med. 2023;42:101193.
5. Ibarra-Estrada M, Kattan E, Aguilera-González P, Sandoval-Plascencia L, Rico-Jauregui U, Gómez-Partida CA, et al. Early adjunctive methylene blue in patients with septic shock: a randomized controlled trial. Crit Care. 2023;27:110.
6. Patel JJ, Willoughby R, Peterson J, Carver T, Zelten J, Markiewicz A, et al. High-dose intravenous hydroxocobalamin (Vitamin B12) in septic shock: a double-blind, allocation-concealed, placebo-controlled single-center pilot randomized controlled trial (the IV-HOCSS trial). Chest. 2022. https://doi.org/10.1016/j.chest.2022.09.021.
7. Auchet T, Regnier M-A, Girerd N, Levy B. Outcome of patients with septic shock and high-dose vasopressor therapy. Ann Intensive Care. 2017;7:43.
8. Belletti A, Musu M, Silvetti S, Saleh O, Pasin L, Monaco F, et al. Non-adrenergic vasopressors in patients with or at risk for vasodilatory shock. A systematic review and meta-analysis of randomized trials. PLoS ONE. 2015;10:e0142605.
9. McIntyre WF, Um KJ, Alhazzani W, Lengyel AP, Hajjar L, Gordon AC, et al. Association of vasopressin plus catecholamine vasopressors vs catecholamines alone with atrial fibrillation in patients with distributive shock: a systematic review and meta-analysis. JAMA. 2018;319:1889–900.
10. Nagendran M, Russell JA, Walley KR, Brett SJ, Perkins GD, Hajjar L, et al. Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials. Intensive Care Med. 2019;45:844–55.
11. Pruna A, Bonaccorso A, Belletti A, Turi S, Di Prima AL, D'amico F, et al. Methylene blue reduces mortality in critically ill and perioperative patients: a meta-analysis of randomized trials. J Cardiothorac Vasc Anesth. 2023. https://doi.org/10.1053/j.jvca.2023.09.037.
12. Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, et al. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med. 2017;377:419–30.
13. Sadjadi M, von Groote T, Weiss R, Strauß C, Wempe C, Albert F, et al. A pilot study of renin-guided angiotensin-ii infusion to reduce kidney stress after cardiac surgery. Anesth Analg. 2024. https://doi.org/10.1213/ANE.0000000000006839.
14. Coulson TG, Miles LF, Serpa Neto A, Pilcher D, Weinberg L, Landoni G, et al. A double-blind randomised feasibility trial of angiotensin-2 in cardiac surgery*. Anaesthesia. 2022;77:999–1009.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
16. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
17. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6.
18. McMaster University (developed by Evidence Prime). GRADEpro GDT 2015.
19. Gaudry S, Messika J, Ricard J-D, Guillo S, Pasquet B, Dubief E, et al. Patient-important outcomes in randomized controlled trials in critically ill patients: a systematic review. Ann Intensive Care. 2017;7:28.
20. Harhay MO, Wagner J, Ratcliffe SJ, Bronheim RS, Gopal A, Green S, et al. Outcomes and statistical power in adult critical care randomized trials. Am J Respir Crit Care Med. 2014;189:1469–78.
21. Walker HGM, Brown AJ, Vaz IP, Reed R, Schofield MA, Shao J, et al. Composite outcome measures in high-impact critical care randomised controlled trials: a systematic review. Crit Care. 2024;28:184.
22. Kotani Y, Di Gioia A, Landoni G, Belletti A, Khanna AK. An updated "norepinephrine equivalent" score in intensive care as a marker of shock severity. Crit Care. 2023;27:29.
23. Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. J Clin Epidemiol. 2008;61:763–9.
24. Albanèse J, Leone M, Delmas A, Martin C. Terlipressin or norepinephrine in hyperdynamic septic shock: a prospective, randomized study. Crit Care Med. 2005;33:1897–902.
25. Arora V, Maiwall R, Rajan V, Jindal A, Muralikrishna Shasthry S, Kumar G, et al. Terlipressin is superior to noradrenaline in the management of acute kidney injury in acute on chronic liver failure. Hepatology. 2020;71:600–10.
26. Barzegar E, Ahmadi A, Mousavi S, Nouri M, Mojtahedzadeh M. The therapeutic role of vasopressin on improving lactate clearance during and after vasogenic shock: microcirculation, is it the black box? Acta Med Iran. 2016;54:15–23.
27. Chawla LS, Busse L, Brasha-Mitchell E, Davison D, Honiq J, Alotaibi Z, et al. Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study. Crit Care. 2014;18:534.
28. Choudhury A, Kedarisetty CK, Vashishtha C, Saini D, Kumar S, Maiwall R, et al. A randomized trial comparing terlipressin and noradrenaline in patients with cirrhosis and septic shock. Liver Int. 2017;37:552–61.
29. Dünser MW, Mayr AJ, Ulmer H, Knotzer H, Sumann G, Pajk W, et al. Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. Circulation. 2003;107:2313–9.

30. Fonseca-Ruiz NJ, Cano ASL, Carmona DPO, Aguirre MC, Gómez Hernández MP, García CO, et al. Uso de vasopresina en pacientes con choque séptico refractario a catecolaminas. Acta Colomb Cuid Intensivo. 2013;13:114–23.
31. Gordon AC, Mason AJ, Thirunavukkarasu N, Perkins GD, Cecconi M, Cepkova M, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. JAMA. 2016;316:509–18.
32. Hajjar LA, Zambolim C, Belletti A, de Almeida JP, Gordon AC, Oliveira G, et al. Vasopressin versus norepinephrine for the management of septic shock in cancer patients: the VANCS II randomized clinical trial. Crit Care Med. 2019;47:1743–50.
33. Hua F, Wang X, Zhu L. Terlipressin decreases vascular endothelial growth factor expression and improves oxygenation in patients with acute respiratory distress syndrome and shock. J Emerg Med. 2013;44:434–9.
34. Hussien RM, El-Gendy HA, Elsaidy MI, Abdelhamid MS, Shabana TS. Comparison between norepinephrine alone versus norepinephrine/vasopressin combination for resuscitation in septic shock: a randomized clinical trial. Egypt J Crit Care Med. 2021;8:58.
35. Kirov MY, Evgenov OV, Evgenov NV, Egorina EM, Sovershaev MA, Sveinbjørnsson B, et al. Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. Crit Care Med. 2001;29:1860–7.
36. Laterre P-F, Berry SM, Blemings A, Carlsen JE, François B, Graves T, et al. Effect of selepressin vs placebo on ventilator- and vasopressor-free days in patients with septic shock: the SEPSIS-ACT Randomized clinical trial. JAMA. 2019;322:1476–85.
37. Lauzier F, Lévy B, Lamarre P, Lesur O. Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial. Intensive Care Med. 2006;32:1782–9.
38. Liu ZM, Chen J, Kou Q, Lin Q, Huang X, Tang Z, et al. Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial. Intensive Care Med. 2018;44:1816–25.
39. Malay MB, Ashton RC Jr, Landry DW, Townsend RN. Low-dose vasopressin in the treatment of vasodilatory septic shock. J Trauma. 1999;47:699–703.
40. Lu Y, Yu H, Liu Q, Yao M, Zhu J. The therapeutic effect of continuous intravenous infusion of methylene blue on patients with septic shock. Natl Med J China. 2019;99:868–71.
41. Memis D, Karamanlioglu B, Yuksel M, Gemlik I, Pamukcu Z. The influence of methylene blue infusion on cytokine levels during severe sepsis. Anaesth Intensive Care. 2002;30:755–62.
42. Morelli A, Ertmer C, Lange M, Dünser M, Rehberg S, Van Aken H, et al. Effects of short-term simultaneous infusion of dobutamine and terlipressin in patients with septic shock: the DOBUPRESS study. Br J Anaesth. 2008;100:494–503.
43. Morelli A, Ertmer C, Rehberg S, Lange M, Orecchioni A, Cecchini V, et al. Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. Crit Care. 2009;13:R130.
44. Russell JA, Vincent J-L, Kjølbye AL, Olsson H, Blemings A, Spapen H, et al. Selepressin, a novel selective vasopressin V1A agonist, is an effective substitute for norepinephrine in a phase IIa randomized, placebo-controlled trial in septic shock patients. Crit Care. 2017;21:213.
45. Russell JA, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med. 2008;358:877–87.
46. Sahoo P, Kothari N, Goyal S, Sharma A, Bhatia PK. Comparison of norepinephrine and terlipressin vs norepinephrine alone for management of septic shock: a randomized control study. Indian J Crit Care Med. 2022;26:669–75.
47. Senthilnathan M, Cherian A, Balachander H, Maroju NK. Role of methylene blue in the maintenance of postinduction hemodynamic status in patients with perforation peritonitis: a pilot study. Anesth Essays Res. 2017;11:665–9.
48. Svoboda P, Scheer P, Kantorová I, Doubek J, Dudra J, Radvan M, et al. Terlipressin in the treatment of late phase catecholamine-resistant septic shock. Hepatogastroenterology. 2012;59:1043–7.
49. Wang J, Shi M, Huang L, Li Q, Meng S, Xu J, et al. Addition of terlipressin to norepinephrine in septic shock and effect of renal perfusion: a pilot study. Ren Fail. 2022;44:1207–15.
50. Xiao X, Zhang J, Wang Y, Zhou J, Zhu Y, Jiang D, et al. Effects of terlipressin on patients with sepsis via improving tissue blood flow. J Surg Res. 2016;200:274–82.
51. Bennett SR, McKeown J, Drew P, Griffin S. Angiotensin in cardiac surgery: efficacy in patients on angiotensin converting enzyme inhibitors. Eur J Heart Fail. 2001;3:587–92.
52. Hajjar LA, Vincent JL, Barbosa Gomes Galas FR, Rhodes A, Landoni G, Osawa EA, et al. Vasopressin versus norepinephrine in patients with vasoplegic shock after cardiac surgery: the VANCS randomized controlled trial. Anesthesiology. 2017;126:85–93.
53. Levin RL, Degrange MA, Bruno GF, Del Mazo CD, Taborda DJ, Griotti JJ, et al. Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. Ann Thorac Surg. 2004;77:496–9.
54. Luckner G, Dünser MW, Stadlbauer K-H, Mayr VD, Jochberger S, Wenzel V, et al. Cutaneous vascular reactivity and flow motion response to vasopressin in advanced vasodilatory shock and severe postoperative multiple organ dysfunction syndrome. Crit Care. 2006;10:R40.
55. Maslow AD, Stearns G, Butala P, Schwartz CS, Gough J, Singh AK. The hemodynamic effects of methylene blue when administered at the onset of cardiopulmonary bypass. Anesth Analg. 2006;103:2–8.
56. Morales DLS, Garrido MJ, Madigan JD, Helman DN, Faber J, Williams MR, et al. A double-blind randomized trial: prophylactic vasopressin reduces hypotension after cardiopulmonary bypass. Ann Thorac Surg. 2003;75:926–30.
57. Okamoto Y, Nohmi T, Higa Y, Seki K, Yamashita A. Vasopressin does not raise cardiac enzymes following cardiac surgery: a randomized double-blind clinical trial. J Cardiothorac Vasc Anesth. 2015;29:46–51.
58. Ozal E, Kuralay E, Yildirim V, Kilic S, Bolcal C, Kücükarslan N, et al. Preoperative methylene blue administration in patients at high risk for vasoplegic syndrome during cardiac surgery. Ann Thorac Surg. 2005;79:1615–9.
59. Papadopoulos G, Sintou E, Siminelakis S, Koletsis E, Baikoussis NG, Apostolakis E. Perioperative infusion of low- dose of vasopressin for prevention and management of vasodilatory vasoplegic syndrome in patients undergoing coronary artery bypass grafting–a double-blind randomized study. J Cardiothorac Surg. 2010;5:17.
60. Deng Y, Wang R, Li S, Zhu X, Wang T, Wu J, et al. Methylene blue reduces incidence of early postoperative cognitive disorders in elderly patients undergoing major non-cardiac surgery: an open-label randomized controlled clinical trial. J Clin Anesth. 2021;68:110108.
61. Elgebaly AS, Abd El Ghafar MS, Fathy SM, Shaddad MN. Vasopressin continuous infusion improves intracranial pressure and patient outcomes after surgical clipping or endovascular coiling of cerebral aneurysm. Anesth Essays Res. 2019;13:528–34.
62. Hong SH, Lee JM, Choi JH, Chung HS, Park JH, Park CS. Perioperative assessment of terlipressin infusion during living donor liver transplantation. J Int Med Res. 2012;40:225–36.
63. Huang J, Gao X, Wang M, Yang Z, Xiang L, Li Y, et al. Prophylactic administration with methylene blue improves hemodynamic stabilization during obstructive jaundice-related diseases' operation: a blinded randomized controlled trial. J Gastrointest Surg. 2023;27:1837–45.
64. Koelzow H, Gedney JA, Baumann J, Snook NJ, Bellamy MC. The effect of methylene blue on the hemodynamic changes during ischemia reperfusion injury in orthotopic liver transplantation. Anesth Analg. 2002;94:824–9.
65. Kohler A, Perrodin S, De Gottardi A, Candinas D, Beldi G. Effectiveness of terlipressin for prevention of complications after major liver resection–a randomized placebo-controlled trial. HPB. 2020;22:884–91.
66. Mahdy MM, Abbas MS, Kamel EZ, Mostafa MF, Herdan R, Hassan SA, et al. Effects of terlipressin infusion during hepatobiliary surgery on systemic and splanchnic haemodynamics, renal function and blood loss: a double-blind, randomized clinical trial. BMC Anesthesiol. 2019;19:106.
67. Reddy MS, Kaliamoorthy I, Rajakumar A, Malleeshwaran S, Appuswamy E, Lakshmi S, et al. Double-blind randomized controlled trial of the routine perioperative use of terlipressin in adult living donor liver transplantation. Liver Transpl. 2017;23:1007–14.
68. Song T, Kim MK, Kim M-L, Jung YW, Yun BS, Seong SJ. Use of vasopressin vs epinephrine to reduce haemorrhage during myomectomy: a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol. 2015;195:177–81.
69. Zhang L, Tian M, Sun L-Y, Zhu Z-J. Prophylactic terlipressin infusion for severe postreperfusion syndrome in patients undergoing deceased

donor liver transplantation: the TIPS-DDLT randomized controlled trial. Int J Surg. 2023;109:1923–31.
70. Hasija S, Makhija N, Choudhury M, Hote M, Chauhan S, Kiran U. Prophylactic vasopressin in patients receiving the angiotensin-converting enzyme inhibitor ramipril undergoing coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth. 2010;24:230–8.
71. Jiang L, Sheng Y, Feng X, Wu J. The effects and safety of vasopressin receptor agonists in patients with septic shock: a meta-analysis and trial sequential analysis. Crit Care. 2019;23:91.
72. Dünser MW, Bouvet O, Knotzer H, Arulkumaran N, Hajjar LA, Ulmer H, et al. Vasopressin in cardiac surgery: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2018;32:2225–32.
73. Heybati K, Xie G, Ellythy L, Poudel K, Deng J, Zhou F, et al. Outcomes of vasopressin-receptor agonists versus norepinephrine in adults with perioperative hypotension: a systematic review. J Cardiothorac Vasc Anesth. 2024;38:1577–86.
74. Zhong L, Ji X-W, Wang H-L, Zhao G-M, Zhou Q, Xie B. Non-catecholamine vasopressors in the treatment of adult patients with septic shock-evidence from meta-analysis and trial sequential analysis of randomized clinical trials. J Intensive Care. 2020;8:83.
75. Fernando SM, Tran A, Soliman K, Flynn B, Oommen T, Wenzhe L, et al. Methylene blue in septic shock: a systematic review and meta-analysis. Crit Care Explor. 2024;6:e1110.
76. Joannidis M, Druml W, Forni LG, Groeneveld ABJ, Honore PM, Hoste E, et al. Prevention of acute kidney injury and protection of renal function in the intensive care unit: update 2017: expert opinion of the working group on prevention, AKI section, European society of intensive care medicine. Intensive Care Med. 2017;43:730–49.
77. Tumlin JA, Murugan R, Deane AM, Ostermann M, Busse LW, Ham KR, et al. Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. Crit Care Med. 2018;46:949–57.
78. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the global burden of disease study. Lancet. 2020;395:200–11.
79. Gordon AC, Alipanah-Lechner N, Bos LD, Dianti J, Diaz JV, Finfer S, et al. From ICU syndromes to ICU subphenotypes: consensus report and recommendations for developing precision medicine in the ICU. Am J Respir Crit Care Med. 2024;210:155–66.
80. Bellomo R, Forni LG, Busse LW, McCurdy MT, Ham KR, Boldt DW, et al. Renin and survival in patients given angiotensin II for catecholamine-resistant vasodilatory shock. A clinical trial. Am J Respir Crit Care Med. 2020;202:1253–61.
81. Roth D, Heidinger B, Havel C, Herkner H. Different mortality time points in critical care trials: current practice and influence on effect estimates in meta-analyses. Crit Care Med. 2016;44:e737–41.
82. Wieruszewski PM, Leone M, Kaas-Hansen BS, Dugar S, Legrand M, McKenzie CA, et al. Position paper on the reporting of norepinephrine formulations in critical care from the society of critical care medicine and European society of intensive care medicine joint task force. Crit Care Med. 2024;52:521–30.

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